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Original Article

Use of convalescent plasma to treat COVID-19: case studies

Uso de plasma convalescente para tratar COVID-19: estudos de caso

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Abstract

There have been several efforts to minimize the effects caused by the COVID-19 virus around the world. Vaccines were developed in record time and alternative therapies were studied and applied in several countries, such as the use of plasma from recovered patients. Identifying, systematically evaluating and summarizing the best available scientific evidence on the efficacy and safety of using plasma from recovered COVID-19 patients remains the objective of this study. The studies carried out showed that the application of convalescent plasma contributes to the reduction of mortality, viral load and length of hospital stay. However, the effectiveness of the therapy still raises doubts due to the number of patients evaluated in clinical studies, in addition to its high cost and limitations in terms of availability and implementation, with the drug being authorized only for hospital use.

Keywords: COVID-19, treatment therapies, convalescent plasma.

Resumo

Houve vários esforços para minimizar os efeitos causados pelo vírus COVID-19 em todo o mundo. As vacinas foram desenvolvidas em tempo recorde e terapias alternativas foram estudadas e aplicadas em vários países, como o uso de plasma de pacientes recuperados. Identificar, avaliar sistematicamente e resumir as melhores evidências científicas disponíveis sobre a eficácia e segurança do uso de plasma de pacientes recuperados com COVID-19 continua sendo o objetivo deste estudo. Os estudos realizados mostraram que a aplicação de plasma convalescente contribui para a redução da mortalidade, carga viral e tempo de internação hospitalar. No entanto, a eficácia da terapia ainda gera dúvidas devido ao número de pacientes avaliados em estudos clínicos, além de seu alto custo e limitações em termos de disponibilidade e implementação, sendo o medicamento autorizado apenas para uso hospitalar.

Palavras-chave: COVID-19, terapias de tratamento, plasma convalescente.

1. Introduction

The outbreak of the COVID-19 disease that occurred in December 2019 has spread across the world and has become a global pandemic (WHO, 2020). Although the estimated death rate of COVID-19 was lower than that of SARS and MERS, the number of deaths associated with COVID-19 has already surpassed those of SARS and MERS due to the extremely high transmissibility of SARS-CoV-2. Currently, no vaccine or licensed drug is available to prevent or treat COVID-19 infection, and the most infected patients have been treated with respirators (Wu et al., 2020).

Vaccines are being used to decrease severe hospitalizations, but specific antiviral drugs are not available, so it is urgent to look for an alternative strategy for the treatment of COVID-19, especially among critically ill patients (Duan et al., 2020). As the global COVID-19 pandemic continues, transfusion of convalescent plasma or serum from recovered patients has also been considered a promising therapy for prophylaxis of infection or treatment of disease (Casadevall and Pirofski, 2020). Patients who have recovered from COVID-19 with a high titer of neutralizing antibodies can be a valuable source of donor convalescent plasma. However, the potential clinical benefit and risk of convalescent blood products in COVID-19 remains unclear (Duan et al., 2020).

Human convalescent serum could be an option for the prevention and treatment of COVID-19, which could be quickly available when enough people recover and can donate immunoglobulin-containing serum (Casadevall and Pirofski, 2020). Importantly, the use of convalescent plasma or serum was also suggested by the World Health Organization (WHO, 2021) under the Blood Regulators Network when vaccines and antiviral drugs were not available for an emerging virus (Zhang and Liu, 2020).

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2. Active Antibody Therapy

Passive antibody therapy has a history dating back to the 1890s and was the only means of treating certain infectious diseases before the development of antimicrobial therapy in the 1940s. (Casadevall et al., 2004). Convalescent plasma therapy is a classic adaptive immunotherapy that has been applied to the prevention and treatment of infectious viral diseases such as Machupo virus (Bolivian hemorrhagic fever) (Stinebaugh et al., 1966), Junin virus (Argentine hemorrhagic fever) (Ruggiero et al., 1986), Lassa fever (Frame et al., 1984) e Ebola virus (Van Griensven et al., 2016; Kreil, 2015; Mupapa et al., 1999), SARS-CoV virus (Wong et al., 2003), and influenza virus (Zhou et al., 2007). A meta-analysis of 32 studies on SARS coronavirus infection and severe influences showed a statistically significant reduction in the combined odds of mortality after convalescent plasma therapy compared with placebo or no therapy (Mair-Jenkins et al., 2015).

Active antibody therapy involves the administration of antibodies from an individual (who has already had the disease and developed antibodies) to the other (who has not been infected and/or the body is having difficulty fighting the infection), in order to prevent or treating an infectious disease by enhancing recipient immunity. On the other hand, active vaccination requires the induction of an immune response that takes time to develop and varies according to the vaccine recipient. Thus, passive immunization (transfer of antibodies produced by another human being who has already been cured of the infection) of antibodies is the only means of providing immediate immunity to susceptible people. (Casadevall et al., 2004).

Despite the potential usefulness of passive antibody treatments, there have been concerted efforts to use them as initial therapies against emerging and pandemic infectious threats. The absence of large trials certainly contributes to the hesitancy to employ this treatment. Furthermore, the most effective formulations (convalescent plasma or hyperimmune globulin, H-Ig) are unknown. Convalescent plasma has the advantage that while its antibodies limit viral replication, other components of the plasma can also exert beneficial effects, such as replenishing clotting factors, when administered to patients with hemorrhagic fevers such as Ebola (Casadevall and Pirofski, 2020; Kraft et al., 2015; Leider et al., 2010).

On the other hand, individual units of convalescent plasma demonstrate donor-dependent variability in specificities and antibody titers. H-Ig preparations, on the other hand, contain standardized doses of antibodies, although fractionation removes IgM, which may be necessary against some viruses. However, building a strategic stockpile of pathogen-reducing frozen plasma collected from Ebola convalescent patients with well-characterized viral neutralizing activities is an example of how to proceed despite existing unknowns (Dean et al., 2020).

For passive antibody therapy to be effective, it must be administered in a sufficient amount of antibodies. When given to a susceptible person, the antibody circulates in the blood, reaches tissues and protects against infections. Depending on the amount and composition of the antibody, the protection provided by the immunoglobulin can last from weeks to months (Casadevall and Pirofski, 2020). It is important to note that human plasma transfusion is a routine daily event in modern hospitals. Human anti-SARS-CoV-2 plasma differs from standard plasma only by virtue of the presence of antibodies against SARS-CoV-2. Donors will meet all criteria for blood donation based on federal and state regulations for voluntary donor eligibility and will be collected from FDA-licensed blood centers (Food and Drug Administration) (Bloch et al., 2020).

The use of convalescent plasma provides for the neutralization of active viruses, strengthening the immunity of infected patients. In the case of SARS-CoV-2, the mechanism of action by passive antibody therapy would mediate viral protection and neutralization. However, other mechanisms may be possible, such as antibody-dependent cellular cytotoxicity and/or phagocytosis. Possible sources of antibodies to SARS-CoV-2 are from human convalescent sera from individuals who have recovered from COVID-19, monoclonal antibodies (mAbs) or preparation generated in animal hosts, e.g. genetically modified cows that produce human antibodies (Beigel et al., 2018).

Although many types of preparations are under development, the only type of antibody available is that found in human convalescent sera (Figure 1), as more individuals come into contact with COVID-19 and recover, the number of potential donors increases (Casadevall and Pirofski, 2020).

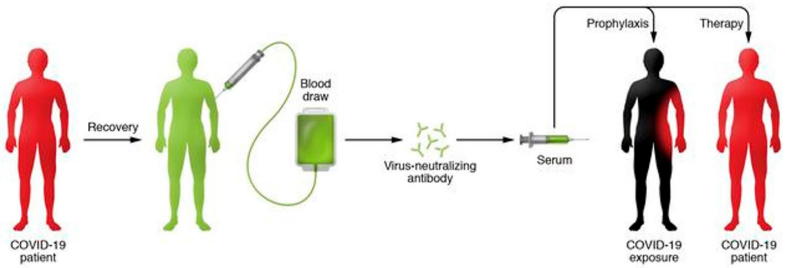

Figure 1. Scheme for using convalescent plasma for COVID-19. An individual who has had COVID-19 and has recovered has their blood drawn and screened for virus neutralizing antibodies. Once identified, high levels of virus neutralizing antibodies can be administered prophylactically to prevent infections in high-risk cases in vulnerable individuals with underlying medical conditions, healthcare professionals and individuals with exposure to confirmed COVID-19 cases. In addition, convalescent serum can potentially be used in individuals with clinical illness to reduce symptoms and mortality. The effectiveness of this approach is not known, but historical experience suggests that convalescent sera may be more effective in preventing disease than in treating established disease.
Source: Casadevall and Pirofski (2020).

Convalescent serum was used during the 2009-2010 H1N1 influenza virus pandemic. Convalescent serum antibodies obtained by apheresis were used to treat individuals with severe H1N1 virus infection who required intensive care. Serum-treated subjects manifested reduced respiratory viral load, serum responses to cytokines, and lower mortality (Hung et al., 2011).

Neutralizing antibodies (NAbs) play important roles in the elimination of viruses and have been considered as an important immunological product for protection or treatment against viral diseases. Virus-specific NAbs, induced by infection or vaccination, have the ability to block viral infection. The level of NAbs has been used as the gold standard for evaluating the effectiveness of vaccines against smallpox, polio, and influenza viruses (Zinkernagel, 2003). The efficacy of passive antibody therapy was associated with the concentration of NAbs in plasma or antibodies from recovered donors (Casadevall and Pirofski, 2020).

3. Convalescent Plasma Therapy Versus COVID-19

The common clinical and laboratory symptoms of COVID-19 are similar and difficult to distinguish from pneumonia caused by other pathogens and common to the respiratory tract. Currently, PCR-based viral RNA detection is almost the only way to confirm the diagnosis of SARS-CoV-2 infection (Wu et al., 2020). Compared to PCR testing, serological testing is advantageous with faster turnaround time, high throughput and less workload. However, the clinical value of antibodies largely depends on understanding the host's antibody responses during infection. SARS-CoV-2 is an emerging virus, the antibody response in COVID-19 patients is unknown.

Second Roback and Guarner (2020), to meet the growing demand of COVID-19 cases, one approach would be to combine the use of convalescent plasma and H-Ig in a complementary way to treat infected patients in the current pandemic and subsequent waves of infections, defining the following considerations:

1. Blood centers could start collecting plasma from convalescent donors, preferably at the leading edge of the infectious wave; healthcare workers could encourage patients infected with COVID-19 to donate after hospital discharge. The plasma would be tested, frozen and distributed to hospitals, taken out for simultaneous investigations;
2. A few days after collection, physicians could transfuse convalescent plasma to infected patients. This approach is expected to be most effective in patients before they develop a humoral response to COVID-19. Serological tests that detect COVID-19 neutralizing antibodies would be beneficial in identifying the best treatment candidates. Monitoring patient responses by clinical, laboratory, and imaging results can be compared to antibody titers, specifically, and neutralizing activities in paired plasma samples to develop better algorithms to identify patient and donor factors that predict clinical efficacy;
3. Fund plasma collection capacities, encourage academic, industry and government research, mobilizing efforts. Convalescent plasma transfusion will be limited in scope as transfusions are performed in a hospital setting and may require large infusion volumes. Plasma implantation is associated with adverse events, ranging from mild fever and allergic reactions to life-threatening bronchospasm, transfusion-related acute lung injury, and circulatory overload in patients with cardiorespiratory disorders, which should be carefully screened (Leider et al., 2010). Small risk of transmission of infectious diseases;
4. Dynamic modeling of COVID-19 infections and factors associated with clinical efficacy can be used to inform the distribution of convalescent plasma (and donors) between blood centers and the plasma industry to obtain a COVID H-Ig concentrate -19;
5. Possibility of using small volume H-Ig preparations in laboratory, clinical and hospital environments. Concentrated H-Ig preparations are a time-tested, injectable treatment for viral (eg, hepatitis A and B) and bacterial (eg, tetanus, diphtheria) diseases. In principle, each administered dose prepared from specific antibodies determined for COVID-19 would be simpler than plasma for worldwide distribution. For convalescent plasma, it will be critical to identify factors that predict responses to COVID-19 H-Ig, and to track adverse events.

4. Legislation/guidance on the Use of Convalescent Plasma in Patients with COVID-19

The US Food and Drug Administration (FDA) has approved the use of plasma from recovered patients to treat people suffering from COVID-19, as long as doctors get approval over the phone. The FDA's decision came a day after New York Governor Andrew Cuomo said the state health department would begin treating critically ill patients with convalescent plasma. New York officials said they would recruit patients who have recovered from COVID-19, likely from suburban New York City, where the state's outbreak began, NBC News reported (Tanne, 2020).

On March 24, 2020, the FDA (2020) published guidance to provide recommendations to healthcare providers and investigators regarding the administration and study of investigational convalescent plasma collected from individuals who have recovered from COVID-19 (COVID-19 convalescent plasma) during the public health emergency. The guidance provides recommendations on:

- avenues for use of COVID-19 investigative convalescent plasma;
- patient eligibility;
- COVID-19 convalescent plasma collection, including donor eligibility and qualifications;
- labeling;
- record keeping.

In this recommendation, the FDA clarifies the possible avenues available to administer or study the use of COVID-19 convalescent plasma (FDA, 2020).

In Brazil, the National Health Surveillance Agency (ANVISA in portuguese Agência Nacional de Vigilância Sanitária) recently published a technical note to guide researchers and doctors on the use of convalescent plasma as an experimental treatment for COVID-19, a disease caused by the new coronavirus (SARS-CoV-2).

ANVISA emphasizes that, as these are experimental procedures, study protocols must follow the provisions of Brazilian resolutions applicable to research in human beings. It is also emphasized that the National Research Ethics Commission (CONEP in Portuguese Comissão Nacional de Ética em Pesquisa) decided that all research protocols related to COVID-19 should be sent directly for ethical consideration by CONEP itself, on an emergency basis. Researchers or medical teams must contact the hemotherapy services to formalize possible partnerships to obtain convalescent plasma, according to research protocols or clinical protocols in development, strictly following the technical criteria applicable to donation, processing, storage and blood transfusion, performed in hemotherapy services, as defined by ANVISA and the Ministry of Health. ANVISA also emphasizes that if the intended use involves the use of convalescent plasma as a blood component, it is not possible to submit a clinical study for consideration and prior approval by ANVISA.

According to the technical standard (Brasil, 2020, p. 2):

> [...] the procedure must have its effectiveness approved by the Federal Council of Medicine (CFM), by the Ministry of Health, or it must be used on an experimental basis, upon adherence to the norms established for conducting research on human beings in Brazil, or also, in special situations - considering the public health emergency, the severity of the disease and also, a condition of imminent risk to the patient's life, the decision to use convalescent plasma for COVID-19, under the responsibility of the medical professional, with clarification to the patients of the experimental nature and the risks involved, with the consent of the patient or their family members, in accordance with the production and quality rules applied in hemotherapy services, health care services and the requirements for patient safety.

This standard also mentions that, in these cases, all requirements contained in RDC No. 34/2014 (Brasil, 2014) and in Consolidation Ordinance No. 512, of September 28, 2017, Annex IV, as well as in specific and updated definitions of the Applicable ANVISA and Ministry of Health.

5. Clinical Studies on Convalescent Plasma Treatment in the Fight Against SARS and SARS-CoV-2

Viremia peaks within the first week of infection in most viral diseases (Wu et al., 2020). In a study carried out by Cheng et al. (2005), the authors reported that patients who received convalescent plasma in Hong Kong during an SARS outbreak in 2003. The authors argue that, for most viral infections, peak viremia occurs within the first week of infection and that a primary immune response is develops in about 10 to 14 days, followed by shedding of the virus. Therefore, plasma therapy of recovered patients should be used early. Although this investigation was not randomized, among the 1775 patients, the 80 who received convalescent plasma had a mortality of 12.5%, compared to the overall SARS-related mortality for inpatients (n=299, with 17% of mortality). Antibodies and plasma transfusion volumes varied and did not appear to correlate with clinical response. However, patients who received transfusions within 14 days of symptom onset (n=33) had the best results. The patient usually develops a primary immune response on days 10 to 14, which is followed by shedding of the virus. Therefore, theoretically, it should be more effective to administer convalescent plasma at an early stage of the disease. Patients treated before 14 days had a better prognosis with discharge before 22 days. No immediate adverse effects were observed with the infusion of convalescent plasma. There was no correlation between clinical outcome and plasma infuser volume or coronavirus antibody titers of donors.

Still on the study of Cheng et al. (2005), the amount of antibodies administered to each patient was not standardized. This may have contributed to variations in clinical outcome and a placebo group has not yet been used for comparison. The authors warn of the potential risk of transfusion-transmitted infection. They suggest that, ideally, convalescent plasma should undergo a viral activation procedure before being injected into recipients. However, other treatments may have an effect on the relationship between convalescent plasma and antibody levels, including antiviral drugs, steroids, and intravenous immunoglobulin (Luke et al., 2006).

Bloch et al. (2020) conducted a study to determine whether convalescent plasma transfusion may be beneficial in the treatment of critically ill coronavirus (SARS-CoV-2) patients with severe acute respiratory syndrome. This study was carried out at the infectious diseases department of the Shenzhen Third People's Hospital in Shenzhen, China, from January 20, 2020 to March 25, 2020; the final follow-up date was March 25, 2020. Five critically ill patients with COVID-19 and acute respiratory distress syndrome (ARDS) met the following criteria: severe pneumonia with rapid progression and a continuously high viral load despite antiviral treatment; PAO2/FIO2<300 (blood pressure/inspiratory oxygen fraction); and mechanical ventilation. All 5 were treated with convalescent plasma transfusion. Clinical outcomes were compared before and after convalescent plasma transfusion. Patients were transfused with convalescent plasma with a SARS-CoV-2-specific antibody-binding (IgG) titer greater than 1:1000 (end-point dilution titer by enzyme-linked immunosorbent assay (ELISA) and an enzyme-linked immunosorbent assay (ELISA) titer). neutralization greater than 40 (end point dilution titer) obtained in 5 patients who recovered from COVID-19. Convalescent plasma was administered between 10 and 22 days after admission. Changes in body temperature, score on the Sequential Assessment of Bankruptcy of Organs (SOFA) (range 0 to 24, with higher scores indicating more severe disease), PAO2/FIO2, viral load, serum antibody titer, routine blood chemistry index, ARDS and ventilation, and extracorporeal membrane oxygenation (ECMO)) were verified before and after convalescent plasma transfusion. All five patients (age range 36 to 65 years; two women) were on mechanical ventilation at the time of treatment and all received agen antiviral drugs and methylprednisolone.

After plasma transfusion, body temperature normalized within 3 days in 4 of 5 patients, SOFA score decreased, and PAO2/FIO2 increased within 12 days (range: 172-276 before and 284-366 after). Viral loads also decreased and became negative 12 days after transfusion, ELISA-specific titers for SARS-CoV-2 and neutralizing antibodies increased after transfusion (range 40-60 before and 80-320 on day 7). ARDS resolved in 4 patients by 12 days after transfusion and 3 patients were off mechanical ventilation within 2 weeks of treatment. Of the 5 patients, 3 were discharged (length of stay: 53, 51 and 55 days) and 2 were in a stable condition at 37 days after transfusion. In this preliminary uncontrolled case series of 5 critically ill patients with COVID-19 and ARDS, administration of convalescent plasma containing neutralizing antibody was followed by improvement in their clinical status. The authors concluded that the limited sample size precludes a definitive statement about the effectiveness of this treatment and better observations require evaluation in clinical trials (Bloch et al., 2020).

Wu et al. (2020) published a study that included 175 adult patients with COVID-19 admitted to the Shanghai Public Health Clinical Center. Plasma from these recovered patients with mild symptoms was analyzed. Peak binding antibody in plasma was determined by ELISA test. The levels and time course of specific SARS-CoV-2-NAbs and peak binding antibodies were monitored at the same time. SARS-CoV-2 NAbs failed to cross-react with the SARS-CoV virus. SARS-CoV-2-specific NAbs were detected in patients between the 10th and 15th day after disease onset and remained afterward. NAbs titers were variable in different patients. Elderly and middle-aged patients had significantly higher plasma NAbs titers and spine-binding antibodies than younger patients. Notably, among these patients, there were ten patients whose NAb titers were below the detectable level of the test (ID50: <40); while, on the other hand, two patients had very high NAb titers, with ID50: 15989 and 21567, respectively.

NAb titers correlated positively with plasma CRP levels, but negatively correlated with patients' lymphocyte counts at admission, indicating an association between humoral response and cellular immune response. Variations of SARS-CoV-2-specific NAbs in recovered COVID-19 patients may raise concern about the role of NAbs in disease progression. The correlation of NAb titers with age, lymphocyte count and blood CRP levels suggested that the interaction between the virus and host immune response in coronavirus infections should be further explored for the development of an effective vaccine against the SARS-CoV-2 virus. In addition, NAb titration is useful prior to the use of convalescent plasma for prevention or treatment (Wu et al., 2020).

Confirmed COVID-19 cases were classified according to clinical status, and defined based on the New Coronavirus Pneumonia Prevention and Control Program (4th edition) published by the China National Health Commission (Zhao et al., 2020). Patients were classified as having critical illness (severe acute respiratory syndrome, SARS) or having oxygen saturation <93% and requiring invasive or non-invasive mechanical ventilation. This study recorded a total of 173 COVID-19 cases, where all patients were admitted to Shenzhen Third People's Hospital between January 11 and February 9, 2020 and were willing to donate their blood samples. All recorded cases were confirmed to be infected with SARS-CoV-2 by using real-time RT-PCR (rRT-PCR) on samples collected from the respiratory tract. For all enrolled patients, disease onset date, clinical classification, RNA test results during the hospitalization period, and personal demographic information were obtained from clinical records. This study was reviewed by the Shenzhen Third People's Hospital Ethics Committee (2020-0018) (Zhao et al., 2020).

A total of 173 patients with SARS-CoV-2 infection were included in the tests for serial plasma samples (n=535). Samples were collected during hospitalization and tested for antibodies (Ab), IgM against SARS-CoV-2 (Zhao et al., 2020). This study investigates the dynamics of total antibody (Ab), IgM and IgG antibody against SARS-CoV-2 in serial blood samples collected from patients. In the 173 patients tested, the seroconversion rate for Ab, IgM and IgG was 93.1%, 82.7% and 64.7%, respectively. The reason for the negative values of antibodies, found for 12 patients, can be justified by the collection of blood in the later phase of the disease. The mean time of serum conversion to Ab, IgM and IgG was on the 11th, 12th and 14th day, measured separately. The presence of antibodies was less than 40% among patients between the beginning and one week of treatment, increasing rapidly to 100% (Ab), 94.3% (IgM) and 79.8% (IgG) after 15 days. On the other hand, RNA detection ability decreased from 66.7% (58/87) in samples collected before day 7 to 45.5% (25/55) between days 15-39. The combination of RNA and antibody detections significantly improved the sensitivity of pathogenic diagnosis for COVID-19 ($p<0.001$), even in the initial phase (in the first week) ($p=0.007$). In addition, a higher Ab titer was independently associated with a worsening in the clinical score ($p=0.006$) (Zhao et al., 2020).

Ab, IgM and IgG antibodies against SARS-CoV-2 in plasma samples were tested using enzyme-linked immunosorbent assay (ELISA) kits, following manufacturer information. Antibody detection offered vital clinical information during the course of SARS-CoV-2 infection. The results provided empirical support for the routine application of serological tests in the diagnosis and treatment of patients with COVID-19 (Zhao et al., 2020). Still second Zhao et al. (2020), the diagnosis of antibody assays for different patients is presented in Table 1.

The increase in antibodies is not always accompanied by the release of RNA, especially in the most critically ill patients. The finding suggested that the antibodies might not be enough to eliminate the virus. The present data demonstrate that typical antibody responses to acute viral infection are wildly induced in patients with COVID-19. Total antibody was detected for the first time, followed by IgM and IgG. The seroconversion rate and antibody levels increased rapidly in the first two weeks, the cumulative seropositive rate reached 50% by day 11 and 100% by day 39. Second Zhao et al. (2020), the study provided robust evidence that: i) the acute antibody response in patients with SARS-CoV-2 infection is very similar to many other acute viral infections; ii) serological testing can be a powerful approach to achieving timely diagnosis; iii) total antibody is more sensitive than IgM and IgG to detect SARS-CoV-2 infection.

Table 1. Performance of different detections in samples at different times since the onset of disease in patients.

Days after onset	n	RNA		Ab		IgM		IgG		RNA+Ab	
		n(+)	Sensitivity (%, 95%CI)	n(+)	Sensitivity (%, 95%CI)	n(+)	Sensitivity (%, 95%CI)	n(+)	Sensitivity (%, 95%CI)	n(+)	Sensitivity (%, 95%CI)
Total	173	112[$]	67.1 (59.4, 74.1)	161	93.1 (88.2, 96.4)	143	82.7 (76.2, 88)	112	64.7 (57.1, 71.8)	172	99.4 (96.9, 100.0)
1-7	94	58[$]	66.7 (55.7, 76.4)	36	38.3 (28.5, 48.9)	27	28.7 (19.9, 39.0)	18	19.1 (11.8, 28.6)	74	78.7 (69.1, 86.5)
8-14	135	67[$]	54.0 (44.8, 63.0)	121	89.6 (83.2, 94.2)	99	73.3 (65.0, 80.6)	73	54.1 (45.3, 62.7)	131	97.0 (92.6, 99.2)
15-39	90	25	45.5 (32.0, 59.5)	90	100.0 (96.0, 100.0)	83[*]	94.3 (87.2, 98.1)	71[#]	79.8 (69.9, 87.6)	90	100.0 (96.0, 100.0)

[*]Two patients missed IgM tests due to inadequate plasma samples; [#]One patient missed IgB tests due to inadequate plasma samples; [$]There were 7, 11 and 35 patients had not been performed RNA testing during the 1-7 onset day, 8-14 onset day and 15-39 onset day, respectively.
Source: Zhao et al. (2020).

Duan et al. (2020) explored the feasibility of convalescent plasma transfusion to rescue critically ill patients with COVID-19. In this study, 10 critically ill patients confirmed by real-time viral RNA testing were prospectively included. The median time between disease onset and convalescent plasma transfusion was 16.5 days. A 200 mL dose of convalescent plasma derived from freshly recovered donors with neutralizing antibody titers above 1:640 was transfused within 4 hours to the patients as an adjunct to maximal supportive care and antiviral agents, following the transfusion protocol of WHO (2021) blood.. Results from the 10 severe adult cases showed that the dose (200 mL) of convalescent plasma was well tolerated and could significantly increase or maintain neutralizing antibodies at a high level, leading to disappearance of viremia within 7 days. Meanwhile, clinical symptoms were significantly improved (temperature normalization and dyspnea relief) along with increased oxyhemoglobin saturation within 3 days. Several parameters tended to improve compared to pre-transfusion, including increased lymphocyte counts (0.65 × 109/L vs. 0.76 × 109/L) and decreased C-reactive protein (55.98 mg/L vs. 18.13 mg/L). Radiological examinations showed varying degrees of absorption of the pulmonary lesions in 7 days. Viral load was undetectable after transfusion in seven patients who had previous viremia. No serious adverse effects were observed. This study showed that convalescent plasma therapy was well tolerated and could potentially improve clinical outcome through neutralizing viremia in severe cases of COVID-19. The optimal dose and time point, as well as the clinical benefit of convalescent plasma therapy, need further investigation in a larger, well-controlled study.

Shen et al. (2020) evaluated convalescent plasma transfusion in the treatment of critically ill patients with SARS-CoV2 infection. A series of 5 critically ill patients with COVID-19 and acute respiratory distress syndrome (ARDS), all laboratory-confirmed, and meeting the following criteria: i) severe pneumonia with rapid viral load progression, even despite antiviral treatment; ii) PAO2 (measured in mm Hg)/FIO2<300 (measured as the fraction of inspired oxygen); and iii) mechanical ventilation. All 5 patients were treated with convalescent plasma. The study was carried out by the infectious diseases department of the Shenzhen Third People's Hospital in Shenzhen, China, from January 20, 2020 to March 25, 2020. Serum from each recipient was obtained and tested by the ELISA method (immunosorbent assay enzyme-linked), antibody titers were tested one day before convalescent plasma transfusion. Patients received two consecutive transfusions (200 mL each) of convalescent plasma, according to blood compatibility and on the same day they were obtained from the donor. Patients received antiviral agents continuously until SARS-CoV-2 viral loads became negative. Patients who received convalescent plasma were considered to be in critical condition: i) severe respiratory failure requiring mechanical ventilation; ii) shock, identified by the use of vasopressor therapy and elevated lactate levels (> 2 mmol / L) despite adequate fluid resuscitation; or iii) failure of other organs that require intensive care (ICU) admission (Shen et al., 2020).

Also in the study carried out by Shen et al. (2020), the 5 convalescent plasma donors were aged between 18 and 60 years and had recovered from SARS-CoV-2 infection, were asymptomatic for at least 10 days of COVID-19, tested negative at the time of donation for SARS-CoV-2 and other respiratory viruses, as well as for hepatitis B and C, HIV and syphilis at the time of donation. Donors were tested by ELISA for SARS-CoV-2 greater than 1:1000 and a neutralizing antibody titer greater than 40. Patients who received convalescent plasma were evaluated according to medical system data: i) demographic data; ii) days of hospitalization from the onset of symptoms and their presentation; iii) data on the various treatments, including mechanical ventilation, antiviral and steroid therapies; iv) clinical data including body temperature, PAO2/FIO2 and sequential assessment of organ failure (SOFA) score (range 0 to 24, with higher scores indicating more severe disease); v) laboratory data, including white blood cell count, lymphocyte count, assessment of liver and kidney function, threshold cycle value (Ct, number of cycles required to cross the test threshold, high values are related

to low viral load), inflammatory factors of C-reactive protein (CRP), procalcitonin and IL-6 and serum antibody titers (IgG, IgM and neutralizing antibodies); vi) data from chest imaging studies; vii) information on complications such as acute respiratory distress syndrome (ARDS), bacterial pneumonia, and multiple organ dysfunction syndrome. Ct values for the 5 recipients were measured on the 1st, 3rd, 7th and 12th day after transfusion.

Clinical characteristics of infected patients and comparison of viral load, clinical indices and laboratory results before and after transfusion with convalescent plasma are shown in Table 2 and 3, respectively (Shen et al., 2020).

Figure 2 shows the changes in the ELISA test after convalescent plasma transfusion. IgG and IgM levels increased after transfusion and maintained an elevated level after day 7 (Figure 2A and 2B). The neutralizing antibodies of the 5 receptors increased after the 7th day of the transfusion, as shown in Figure 2C.

The 5 patients were on mechanical ventilation at the time of the transfusion and 3 patients were weaned from mechanical ventilation shortly after the administration of convalescent plasma. Patient 2 was receiving extracorporeal membrane oxygenation (ECMO) and on day 5 after the transfusion he no longer needed it. Some limitations were raised by Shen et al. (2020), how:

- Few cases evaluated.
- //It was unclear whether patients would have improved without convalescent plasma transfusion.
- All patients were treated with various other agents (including antiviral drugs) and it was unclear whether the improvement was due to convalescent plasma alone.
- Plasma transfusion was administered 10 to 22 days after admission, not knowing whether a different period would have different results.
- It is not known whether this approach reduces the death rate.

Table 2. Clinical characteristics of patients infected with SARS-CoV-2 who received convalescent plasma.

	Patient				
	1	**2**	**3**	**4**	**5**
Sex	Male	Male	Female	Female	Male
Age, y	70s	60s	50s	30s	60s
Weight, kg	55	85	60	41.5	87
Smoking	No	No	No	No	No
Blood type	B	B	B	A	B
Coexisting chronic diseases	None	Hypertension; mitral insufficiency	None	None	None
Disease presentation and course					
Estimated incubation period, d[a]	1	7	3	7	15
Interval between symptom onset and admission, d	2	4	2	3	2
Interval between admission and plasma transfusion, d	22	10	20	3	2
Complications prior to plasma transfusion	Bacterial pneumonia; severe ARDS; MODS	Bacterial pneumonia; fungal pneumonia; severe ARDS; myocardial damage	Severe ARDS	Severe ARDS	Severe ARDS
Most severe disease classification	Critical	Critical	Critical	Critical	Critical
Treatments					
Steroids	Methylprednisolone	Methylprednisolone	Methylprednisolone	Methylprednisolone	Methylprednisolone
Antivirais	Lopinavir/ritoavir; interferon alfa-1b; favipiravir	Lopinavir/ritoavir; arbidol; darunavir	Lopinavir/ritoavir; interferon alfa-1b	Interferon alfa-1b; favipiravir	Lopinavir/ritoavir; interferon alfa-1b

Abreviations: ARDS: acute respiratory distress; MODS: multiple organ dysfunction syndrome; SARS-CoV-2: severe acute respiratory syndrome coronavírus 2. [a]Estimated incubation period defined as interval between estimated exposure to SARS-CoV-2 and symptom onset. **Source:** Adapted from Shen et al. (2020).

Table 3. Comparison of viral load, clinical indices and laboratory results before and after transfusion with convalescent plasma.

	Patient				
	1	**2**	**3**	**4**	**5**
Clinical characteristics					
Body temperature, °C					
Just before transfusion	38.6	39.0	37.6	38.3	39.0
Day 1 posttransfusion	38.5	36.8	37.7	37.9	39.0
Day 3 posttransfusion	38.1	36.6	37.0	36.6	36.8
Day 7 posttransfusion	37.8	37.2	36.5	37.9	36.8
Day 12 posttransfusion	37.0	36.8	36.6	36.8	37.9
SOFA score[a]					
Just before transfusion	5	10	3	3	2
Day 1 posttransfusion	4	12	4	3	2
Day 3 posttransfusion	6	10	3	2	2
Day 5 posttransfusion	5	11	2	2	2
Day 7 posttransfusion	3	7	2	2	1
Day 12 posttransfusion	2	4	2	1	1
P_{AO2}/F_{IO2}[b]					
Just before transfusion	276	209	172	188	205
Day 1 posttransfusion	300	134	184	242	292
Day 3 posttransfusion	220	230	164	233	304
Day 7 posttransfusion	245	206	220	290	230
Day 12 posttransfusion	284	316	342	322	366
Ct value[c] (viral load proxy)					
On admission to hospital	23.0	19.7	18.9	38.0	28.0
Lowest value during hospitalization[d] (highest viral load)	19.2	19.7	18.9	26.6	26.5
Just before transfusion	28.5	22.0	33.0	26.6	35.9
Day 1 posttransfusion	30.0	23.7	38.5	28.0	Negative
Day 3 posttransfusion	34.4	25.0	Negative	Negative	Negative
Day 7 posttransfusion	38.0	32.0	Negative	Negative	Negative
Day 12 posttransfusion	Negative	Negative	Negative	Negative	Negative
Mechanical ventilation					
Onset, days before transfusion	11	2	12	9	2
Extubated, days posttransfusion	Intubated	Intubated	2	9	9
ECMO					
Onset, days before transfusion	Not received	1	Not received	Not received	Not received
Removal, days posttransfusion	NA	5	NA	NA	NA
Laboratory findings					
C-reactive protein, mg/L (normal range, <8)					
Before transfusion	163.4	242.8	65	156.0	173.1
Day 1 posttransfusion	146.2	223.0	108.3	NT	186.8
Day 3 posttransfusion	115.1	75.2	78.7	160.8	233.7
Day 5 posttransfusion	31.3	10.4	74.7	NT	260.4
Day 7 posttransfusion	31.2	13.9	6.2	9.6	5.5
Day 12 posttransfusion	5.3	33.1	NT	5.8	3.2
Procalcitonin, ng/mL (normal range, <0.1)					
Before transfusion	1.2	7.3	0.1	0.2	0.2
Day 1 posttransfusion	1.3	19.7	0.1	0.08	0.4
Day 3 posttransfusion	1.6	13.9	0.09	0.07	1.5
Day 5 posttransfusion	0.9	1.8	0.08	NT	0.9
Day 7 posttransfusion	1.1	0.1	0.04	0.04	0.09
Day 12 posttransfusion	0.4	0.2	NT	0.04	0.07
IL-6, pg/mL (normal range, 0-7)					
Before transfusion	70.5	438.2	63.9	79.1	87.8
Day 1 posttransfusion	74.9	NT	118.5	39.3	NT
Day 3 posttransfusion	34.5	1045.0	67.0	25.8	797.9
Day 5 posttransfusion	24.1	334.1	590.5	NT	NT
Day 7 posttransfusion	30.8	29.8	174.3	34.0	69.9
Day 12 posttransfusion	6.1	31.8	NT	2.7	54.9
Length of hospital stay[d]	Remains hospitalized	Remains hospitalized	53	51	55
Current status as of March 25, 2020	Stable, still received mechanical ventilation	Stable, still received mechanical ventilation	Discharged home	Discharged home	Discharged home

Abbreviations: Ct: cycle threshold; ECMO: extracorporeal membrane oxygenation; NT: not tested; NA: not applicable. [a]The SOFA score is calculated using 6 systems: respiratory, coagulation, hepatic, cardiovascular, central nervous system, and kidney. A escore of 0 is given for normal function through to 4 for most abnormal for each system. The worst values on each day are recorded, and the SOFA score is the sum of the scores of each system; [b]P_{AO2}/F_{IO2} ratio was defined as the ratio of the partial pressure of arterial oxygen to the percentage of inspired oxygen. [c]Cycle thresshold is the number of polymerase chain reaction cycles required for gene amplification. A higher Ct value is correlated with a lower viral load. Lowest value (highest viral load) between hospital admission and plasma transfusion; [d]Lowest value (highest viral load) between hospital admission and plasma transfusion.
Source: Adapted from Shen et al. (2020).

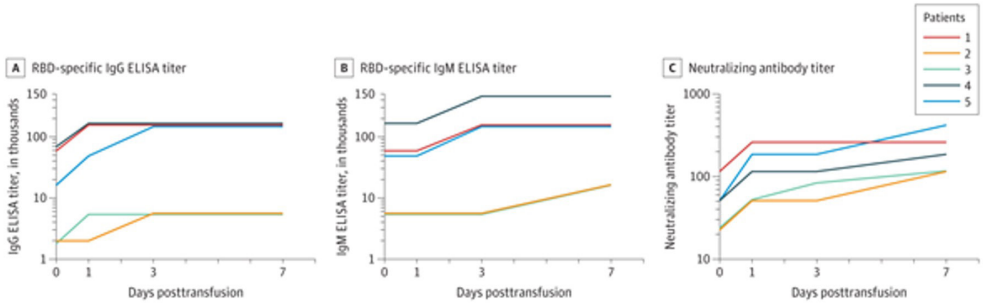

Figure 2. Changes in IgG and IgM ELISA specific for the receptor-binding domain and neutralizing antibody titers before and after convalescent plasma transfusion in patients.
Source: Shen et al. (2020).

Joyner et al. (2021) carried out a study where the levels of anti-SARS-CoV-2 IgG antibodies in convalescent plasma used to treat hospitalized adults with Covid-19 were determined. Of the 3082 patients included in the study, death within 30 days after plasma transfusion occurred in 115 of 515 critically ill patients (22.3%), 549 of 2006 patients (27.4%) in the medium severity patients group and 166 of 561 patients (29.6%) in the low severity group. In the same year, Simonovich et al. (2021) analyzed 228 patients who were assigned to receive convalescent plasma and 105 to receive placebo. They concluded that adverse events and serious adverse events were similar in the two groups and also no significant differences in clinical status or overall mortality were observed between patients treated with convalescent plasma and those receiving placebo.

In January 2022, led by researchers at the NYU Grossman School of Medicine, a study showed that among 2,341 men and women, those who received a convalescent plasma injection shortly after hospitalization were 15% less likely to die within a month of COVID. -19 than those who did not. receiving convalescent plasma or those receiving an inactive saline placebo. Notably, the researchers found that the greatest benefits of the therapy were among patients most at risk for serious complications due to pre-existing conditions such as diabetes or heart disease. The treatment, which contains antibodies and other immune cells needed to fight the infection, also appears to benefit those with type A or AB blood (Troxel et al., 2022).

6. Conclusion

The COVID-19 pandemic represents potentially the biggest global public health crisis since the 1918 pandemic flu outbreak. The speed and volume of worldwide clinical trials launched to investigate potential therapies for COVID-19 highlight the need and ability to produce high-quality evidence, even in the midst of a pandemic.

There is, however, no solid scientific evidence of an effective medication against COVID-19 registered in the world. A survey commissioned by the American Medical Association (AMA) and conducted by the University of Texas (USA) evaluated more than 100 clinical trials of drugs against Sars-CoV-2 and, of these, convalescent plasma therapy has been shown to be efficient, as, second Casadevall & Pirofski (2020), the use of convalescent serum can prevent infection by SARS-CoV-2 in whom it is administered (health professionals), thus avoiding a period of quarantine. Serum can also be a stopgap measure for the current epidemic. The FDA and universities in China and Europe have conducted scientific research on this therapy, and the treatment is routinely applied in European countries, including Germany, Italy, Spain, and the United Kingdom.

In Brazil, studies began in mid-April 2020 with 200 patients. In December 2021, the National Commission for the Incorporation of Technologies in the Unified Health System (CONITEC, 2020 in portuguese Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde) published a recommendation report with the Brazilian Guidelines for Outpatient Drug Treatment of Patients with COVID-19. The document states that treatment with monoclonal antibodies "[...] is expensive, with limitations in terms of availability and implementation, with the drug being authorized only for hospital use, representing a logistical challenge and increasing barriers to adherence and access". In addition, its effectiveness is directly related to the stage of the disease, showing positive results only at the beginning of the infection.

The international consortium of research centers for the development of this study was named Compile (NYU Langone Health, 2021). The countries that integrate the initiative are: United States, Belgium, Brazil, India, Holland and Spain. The most important feature of this study is that it has, in real time, joined data from several surveys from different centers around the world, from randomized and prospective studies, that is, performing a meta-analysis in real time and obtaining these data in a much faster than is normally possible. After all, in a pandemic situation, having speed in responses is very important. So it was shown that, in situations of global epidemiological urgency, this [research] design can be repeated.

Despite having some efficiency, the therapy requires an a priori analysis of the blood collected, as about 30% of patients cured of COVID-19 do not have enough plasma to be collected and transfused to patients carrying the virus. As discussed by Zhao et al. (2020), The acute antibody response in patients with SARS-CoV-2 infection is very similar to many other acute viral infections and total antibody is more sensitive than IgM and IgG to detect SARS-CoV-2 infection.

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